— (c) means for using the measurement of the property of the acoustic energy to modify continued or subsequent application of acoustic energy to the biological materials during the treatment as needed to enhance the treatment.

27. (Twice Amended) A method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or [vessels] vessel in a human or other animal using acoustic energy, comprising:

administering acoustic energy at one or more frequencies by applying a transducer to a site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to [alters] alter transport or cell viability at [an] the internal organ, tissue or vessel.

31. (Amended) The method of claim 27 wherein the transducer is [directly applied to a tissue] placed inside the body using invasive or minimally invasive means.

Please add the following new claims 32 and 33.

32. The method of claim 31 wherein the transducer is placed within a blood vessel using a catheter.

33. The method of claim 31 wherein the transducer is placed within a surgical incision.

Remarks

Applicants and the undersigned greatly appreciate the very helpful interview on December 19, 2001. As discussed, there are two embodiments of the invention: the first is to use ultrasound to alter permeability of molecules through biological materials, by measuring

feedback and modifying the application parameters in "real time". As discussed during the interview, much of the prior art rejection was based on the confusion as to whether or not "time" was one of the variables being measured. Since time is a standard measurement in the prior art, it was not intended to be the sole parameter being measured and used to adjust the applied ultrasound. Rather, parameters of the acoustic energy or an effect of the acoustic energy such as subharmonic pressure, acoustic parameters, temperature, amount or rate of transport of molecules, extent of cavitation, and degree of permeabilization (page 8, lines 5-8) are measured. Claims 1 and 26 have been amended to recite that feedback is obtained during the treatment, so that the ultrasound treatment is enhanced as treatment progresses, as described in the application at page 4, line 1, page 8, lines 1-3 and 9-15. Claim 2 has been amended to delete the reference to measuring the length of time of administration of the acoustic energy, although it is understood that it could be measured in addition to other properties. The prior art only describes application of ultrasound at set parameters, for a defined period of time. The second embodiment is the application of ultrasound so that it alters transport at a distant site - for example, it is applied at the skin, but the effect is at an internal organ, for example, where treatment with a drug is desired. Claim 27 has been amended to more clearly define this distinction, using the language discussed in the interview. As discussed, when ultrasound is applied to the skin in the prior art, it alters permeability of the skin, which can then result in systemic uptake of drug via the blood vessels located underneath the skin. However, the altered permeability is not at the site of the blood vessels, only at the site where the ultrasound is applied. Support for the amendment to claim 31 can find support at lines 29-16 bridging pages 9 and 10. Claim 3 has been amended to

include endogenous organic and inorganic compounds. It is well understood in the art that the term "endogenous" refers to originating or developing within the organism. Support for the amendment to claim 3 can be found, for example, at page 9, lines 8-13.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 9, 17, 19, 20, and 22, were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection in view of the following comments.

As discussed at the interview, claim 9 describes the method where conditions are selected so that the altered permeability is reversible. As in claim 17, which defines the method where conditions are selected so that cavitation occurs, neither is inherent in the method. Conditions can be selected which will permanently alter permeability, and which will not induce cavitation. See, for example, page 7, lines 9-13 and 16-27.

Rejection Under 35 U.S.C. § 102

Claims 1-3, 5, 7, 14, 15, 18, 23, 25 and 26 were rejected under 35 U.S.C. § 102(b) as being anticipated by Tachibana et al., Enhancement of cell killing of HL-60 cells by ultrasound in the presence of the photosensitizing drug Protofrin II", *Cancer Lett.* 72(3):195-199 (1993) ("Tachibana"). Claims 27-28, 30, and 31, were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,445,611 to Eppstein et al. ("Eppstein"). Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

Tachibana, et al.

Tachibana, et al., enhances killing of tumor cells by a drug, photofrin II, a porphyrin, by increasing uptake of the drug using ultrasound. The ultrasound was applied at one of three different intensities. Cell viability was then measured. This is not the claimed method. There is no "real time" feedback contemplated nor demonstrated, allowing adjustment of the ultrasound properties at the time of application. Moreover, there is no measurement of any acoustical property, as clearly required by the amended claims. Therefore Tachibana, et al., fails to disclose the elements of claims 1-3, 5, 7, 14, 15, 18, 23, 25, or 26.

Eppstein

Eppstein teaches using ultrasound to alter drug delivery or transport of analyte from cells in the skin, when the ultrasound is applied transdermally. Eppstein does not teach altering the permeability or viability of cells at a vessel, internal tissue or internal organ, either by direct application of the ultrasound to the membrane, vessel, tissue or organ, or by indirect application via the skin or a mucosal membrane. As discussed with the examiner, merely applying ultrasound to the skin may alter uptake by virtue of the alteration of the permeability of the skin, which increases drug concentration inside the body but it does not alter permeability at a distant site unless one knowingly selects the conditions which would lead to an alteration of the permeability at the distant site. Therefore Eppstein does not anticipate the method of claims 27, 28, 30 or 31.

Rejection Under 35 U.S.C. § 103

Claims 1-6, 8-18, and 23-26 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,636,632 to Bommannan, et al. ("Bommannan"). Claims 1-5, 8-18, and 23-26, were rejected under35 U.S.C. § 103(a) as obvious over Eppstein. Claims 1-5, 8-18, and 23-26 were rejected under 35 U.S.C. § 103(a) as obvious over Ogden. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Bommannan

Bommannan describes application of ultrasound to enhance drug delivery. Bommannan fails to disclose measurement of an acoustic parameter in order to modify the ultrasound application. Even as to the properties that are measured, these are static measurements; they are not used to modify the applied ultrasound. Now that the claims clearly exclude time as the sole measured parameter, there is nothing in Bommannan that would lead one skilled in the art to optimize treatment variables while the treatment is in progress. Bommannan clearly teaches that "real time" feedback is unnecessary - one merely selects conditions and goes with it. This ignores differences in tissue types, amounts of drug to be administered, changes in the physical environment within tissues over time, and other variables that affect drug delivery.

Ogden

Ogden is the same as Eppstein or Bommannan. He discloses a drug delivery system including a means for applying ultrasound (a transducer and a power source), and a control system for adjusting the amount of drug being delivered. However, the control system (see col. 5, line 20 to col. 6, line 36) is not feedback responsive.

Ogden does refer to feedback control at col. 6, lines 37-50. In this embodiment, the treatment is terminated if the blood sugar levels become too high or the temperature at the skin's surface becomes too elevated due to safety concerns. This is distinguished from feedback in the form of a property of acoustic energy leading to optimization of the treatment, making clear that the treatment parameters are adjusted, not terminated.

Eppstein is discussed above. Neither Eppstein nor Ogden make up for the deficiencies of Bommannan. Alone or in combination with any of Ogden or Eppstein, there is no teaching that one should measure an acoustic parameter in real time (other than just time alone) in order to modify the ultrasound being applied. It is well established that for a rejection under section 103, the prior art must not only disclose the claimed elements, but teach one skilled in the art to combine and modify the claimed elements as applicants have done. The prior art simply fails to do so. There is no recognition in any of the art cited by the examiner that acoustic properties can be monitored and then used to provide feedback to control the properties of the applied ultrasound to thereby modify cell permeability or viability. Therefore the methods of claims 1-25, and the device of claim 26, are not obvious.

Marked Up Version of Amended Claims
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method for [altering permeability, cell viability or structural integrity of biological materials] treating cells or biological materials to alter permeability, cell viability or structural integrity comprising

(a) administering acoustic energy to the biological materials at one or more frequencies;

(b) measuring a property or effect of the acoustic energy [at the time of or subsequent to the initial application of the] during the treatment with acoustic energy; and

(c) using the measurement obtained in step (b) to modify continued or subsequent application of acoustic energy to the biological materials during the treatment as needed to enhance the treatment.

2. (amended) The method of claim 1 wherein the property of the acoustic energy being measured in step b is one or more properties selected from the group consisting of pressure at one or more frequencies, and energy input at one or more frequencies[, and length of time the acoustic energy is administered].

3. (amended) The method of claim 1 wherein the acoustic energy is effective to alter permeability of the biological materials to a chemical or biological agent selected from the group consisting of peptides, proteins, sugars, polysaccharides, nucleotides, polynucleotide molecules, synthetic organic compounds, synthetic inorganic compounds, endogenous organic compounds, endogenous inorganic compounds and combinations and aggregates thereof.

4. The method of claim 3 wherein the agent is in a form selected from the group consisting of cells or virus particles, nano or microparticles, liposomes or other lipid vesicles or emulsions.

5. The method of claim 3 wherein the chemical or biological agent is delivered to cells or tissue.

6. The method of claim 3 wherein the chemical or biological agent is detected or quantitated, further comprising

removing biological fluid or molecules simultaneously, previously, or subsequently to the application of acoustic energy, and

assaying the biological fluid or molecules to detect or quantitate the chemical or biological agents.

7. The method of claim 1 wherein the acoustic energy is administered to kill cells.

8. The method of claim 1 wherein the biological materials are made more permeable by the exposure to acoustic energy.

9. (amended) The method of claim 8 wherein the biological materials are made partially or completely reversibly permeable.

10. The method of claim 1 wherein the biological materials are biological membranes.

11. The method of claim 1 wherein the biological material is skin.

12. The method of claim 1 wherein the acoustic energy is applied to biological materials in an amount effective to disaggregate or dissociate the materials.

13. The method of claim 1 wherein the biological materials are blood vessels.

14. The method of claim 1 wherein the acoustic energy is applied at a frequency between 1 kHz and 10 MHz.

15. The method of claim 1 wherein the acoustic energy is ultrasound.

16. The method of claim 1 wherein the acoustic energy is applied at a peak positive pressure of up to 100 atmospheres.

17. (amended) The method of claim 1 wherein the acoustic energy is applied under conditions to effect cavitation within or on the surface of the biological materials.

18. The method of claim 1 further comprising administering an agent to enhance transport within or permeability of the biological materials.

19. (Amended) The method of claim 1 wherein the property of the acoustic energy that is measured is measured at one or more frequencies other than the frequency or frequencies at which the acoustic energy is applied.

20. (Amended) The method of claim 1 wherein the property of the acoustic energy that is measured is measured at a frequency or frequencies corresponding to integer multiples of one-half or one-fourth of the frequency applied.

21. (Amended) The method of claim 1 wherein the acoustic energy is measured at one or more frequencies in the acoustic spectrum which do not correspond to peaks in the acoustic spectrum and are taken from the broadband signal of the acoustic spectrum.

22. (Amended) The method of claim 19 wherein the acoustic energy measurement is analyzed using a mathematical algorithm, selected from the group consisting of Fourier Transform and Fast Fourier Transform.

23. The method of claim 1 wherein the application of the acoustic energy is modified by changing an acoustic parameter selected from the group consisting of pressure, energy, frequency, pulse length, total exposure time, duty cycle, and combinations thereof.

24. The method of claim 1 wherein the application of the acoustic energy is modified by changing a non-acoustic parameter selected from the group consisting of temperature, fluid gas content, administration rate of molecules to be transported, sample collection rate, device position, and combinations thereof.

25. The method of claim 1 wherein the application of the acoustic energy input is modified by interrupting the application.

26. (twice Amended) A device comprising

(a) means for treating cells or biological materials by administering acoustic energy to the cells or biological materials [altering] to alter permeability, cell viability or structural integrity of biological materials at one or more frequencies;

(b) means for measuring a property or effect of the acoustic energy [at the time of or subsequent to the initial application of the] during the treatment with acoustic energy; and

(c) means for using the measurement of the property of the acoustic energy to modify continued or subsequent application of acoustic energy to the biological materials during the treatment as needed to enhance the treatment.

27. (Twice Amended) A method for altering cell viability or transport of chemical or biological agents into or through an internal organ, internal tissue or [vessels] vessel in a human or other animal using acoustic energy, comprising:

administering acoustic energy at one or more frequencies by applying a transducer to a site on the human or other animal other than where transport or cell viability is to be altered;

wherein the acoustic energy is effective to [alters] alter transport or cell viability at [an] the internal organ, tissue or vessel.

28. (Amended) The method of claim 27 wherein the acoustic energy is applied to the skin or a mucosal membrane and alters transport or cell viability at an internal organ, tissue or vessel.

29. (Amended) The method of claim 27 wherein the acoustic energy alters transport or cell viability of tumor cells.

30. (Amended) The method of claim 27 wherein the acoustic energy alters transport into or out of the cells of molecules selected from the group consisting of therapeutic, prophylactic and diagnostic agents.

31. (Amended) The method of claim 27 wherein the transducer is [directly applied to a tissue] placed inside the body using invasive or minimally invasive means.

Please add the following new claims 32 and 33.

32. The method of claim 31 wherein the transducer is placed within a blood vessel using a catheter.

33. The method of claim 31 wherein the transducer is placed within a surgical incision.